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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,669	11/01/2001	Robert H. Broyles	OKL010-107/00727A	5327

32425 7590 10/20/2005

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,669	BROYLES ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,19,22,24,25,26, and 27* is/are pending in the application.

4a) Of the above claim(s) *11,26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19,22,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The affidavits filed 4/13/05 and the Request for reconsideration filed 7/8/05 are acknowledged. It is noted claim 25 has been marked as "presently amended", however applicant fails to identify the amendment. Appropriate correction is required.

Claims 1, 19, 22, 24, 25, and 27 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19, 22, 24, 25, and 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and following.

When determining whether the disclosure satisfies the enablement requirements, the Office has considered the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance presented, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior and post-filing art for the finding of a lack of enablement for the instantly claimed inventions. The *Wands* analysis and supporting specific evidence have been presented previously, and will not reiterated here. What

needs to be emphasized is the analysis is not based on a single factor but all of the factors as a whole.

The arguments presented in the response of 7/8/05 have been grouped and addressed below.

Applicant argued there is no requirement for correction of the disease phenotype-treatment needs not provide a cure, and pharmacological behavior and long-term consequences are not issues within the purview of the PTO.

In response, the Office never requested a cure for the claimed treatment method but a reasonable support commensurate in scope with the claimed invention. The applicant is reminded the statue under 35 U.S.C 112, first paragraph, "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, **AND OF THE MANNER AND PROCESS OF MAKING AND USING IT, IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS** AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION", which is the basis for the evaluation of claimed invention and the very duty of the PTO bestowed by the Congress. Here, the claimed invention requires "*suppressing* sickle cell disease", thus it is applicant's duty to disclose (describe) that the sickle cell disease is indeed being *suppressed* through delivery of an FtH protein to a globin-producing cell. An example of how a disclosure would satisfy the enablement requirement could be found in the following MPEP text as pursuant to an enabling disclosure required by 35 U.S.C 112, first paragraph,

"AN APPLICANT'S SPECIFICATION MUST ENABLE A PERSON SKILLED IN THE ART TO MAKE AND USE THE CLAIMED INVENTION WITHOUT UNDUE EXPERIMENTATION.(...) AS SUCH, THE DISCLOSURE MUST TEACH A PERSON SKILLED IN EACH ART HOW TO MAKE AND USE THE RELEVANT ASPECT OF THE

INVENTION WITHOUT *UNDUE* EXPERIMENTATION. FOR EXAMPLE, TO ENABLE A CLAIM TO A PROGRAMMED COMPUTER THAT DETERMINES AND DISPLAYS THE THREE-DIMENSIONAL STRUCTURE OF A CHEMICAL COMPOUND, THE DISCLOSURE MUST

- ENABLE A PERSON SKILLED IN THE ART OF MOLECULAR MODELING TO UNDERSTAND AND PRACTICE THE UNDERLYING MOLECULAR MODELING PROCESSES; AND
- ENABLE A PERSON SKILLED IN THE ART OF COMPUTER PROGRAMMING TO CREATE A PROGRAM THAT DIRECTS A COMPUTER TO CREATE AND DISPLAY THE IMAGE REPRESENTING THE THREE-DIMENSIONAL STRUCTURE OF THE COMPOUND.

IN OTHER WORDS, THE DISCLOSURE CORRESPONDING TO EACH ASPECT OF THE INVENTION MUST BE ENABLING TO A PERSON SKILLED IN EACH RESPECTIVE ART. (MPEP 2106.B.2, emphasis added)

According to the standard, the disclosure must show that each aspect of the claimed method is indeed enabling, i.e. from delivery of a FtH protein into the nucleus of significant numbers of globin-producing cells, to sufficient repression of the diseased β-globin gene to such extend that at least one symptom of the sickle cell disease has been suppressed, while maintaining the synthesis of a normal β-globin.

Applicants acknowledged that protein therapy and nucleic acid gene therapy are two distinct fields of scientific study, and asserts the *in vitro* ability of the protein and necessary biological effect had been shown.

In response, the effect of administering FtH protein has *not* been shown either *in vitro or in vivo*, either in the specification or in the subsequently submitted new data. The *in vitro* finding disclosed in the specification was based on a transient nucleic acid transformation experiments, and the biological effect shown was limited to suppressing human beta-globin gene transcription in cultured leukemia cells, not suppressing sickle cell disease in a host animal. If one skilled in the art reading the specification would find this disclosure adequately teaches how to make and use the claimed invention as applicants asserted, applicant would not be the inventor because this information already taught by *Picard et al* before the instant filing date. To this end, the applicant

argued *Picard et al* used erythroleukemia cells, not normal human adult red cells, "thus, little weight should be placed on concerns based on this paper". In response, it is noted that applicant also used erythroleukemia cells in the experimentation disclosed in the instant application (Specification, page 37).

Throughout the 7/8/05 response, applicants repeatedly indicated that they have provided proof of principle, and thus implementing the proposed invention would not be questioned by those skilled in the art. In response, the proof of principle has been provided by *Picard et al*, however, as taught in the teachings of *Picard et al*, over-supply of FtH, causes other physiological consequences that may hamper the treatment of sickle cell disease. Moreover, since there is no indication that nuclear FtH is deficient in sickle cell disease, the applicant fails to teach why the nuclear FtH does not already suppress the diseased β-globin and why supplying more FtH is necessary or effective in correcting the diseased phenotype *in vitro or in vivo*. Throughout the history of medicine, it usually takes decades of work from the proof of principle to clinical benefit. This is the reality for understanding and treating sickle cell disease as taught by *Mankad* (See page 11 of the previous Office action mailed 11/3/04), who teaches after 50 years of investigation since the identification of underlying mechanism of the sickle cell disease, a satisfactory treatment has yet to become reality. Applicants are reminded that the court has held, "[U]NLESS AND UNTIL A PROCESS IS REFINED AND DEVELOPED TO THIS POINT-WHERE SPECIFIC BENEFIT EXISTS IN CURRENTLY AVAILABLE FORM-THERE IS INSUFFICIENT JUSTIFICATION FOR PERMITTING AN APPLICANT TO ENGROSS WHAT MAY PROVE TO BE A BROAD FIELD. . . . A PATENT IS NOT A HUNTING LICENSE. . . .[I]T IS NOT A REWARD FOR THE SEARCH, BUT COMPENSATION FOR ITS SUCCESSFUL CONCLUSION". *Brenner v. Manson*, 148 USPQ 689, 696

(US SupCt., 1966). In the instant case, proof of principle does not equal to a currently available method of suppressing sickle cell disease. The applicants proposed a new therapeutic approach to the treatment of the sickle cell disease based on a preliminary *in vitro* nucleic acid transformation assay, which awaits further development and refinement to the practical level where a clinical benefit becomes reality available to the public. This has yet to come at this date long after the instant priority date.

Applicants then argued the specification contemplates one can deliver the ferritin-H peptide or a truncated form for therapy, and speculating "It is **likely** that a single subunit (21kD) or peptide fragment thereof (12-14 kD) will not require a special transport system, and will avoid the endosomal system". In response, speculation would not meet the standard under 35 U.S.C 112, first paragraph, which requires "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, **AND OF THE MANNER AND PROCESS OF MAKING AND USING IT, IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS** AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION". Further, the claims encompass any form of ferritin H contact with a globin-producing cell, including the whole ferritin molecule, and are not limited to the single subunit or truncated form.

As to the translocation of the FtH from cytoplasma to nucleus, applicant cited a 1999 *Thompson*'s abstract as support indicating that H ferritin was selectively taken up into the nucleus. The abstract was not attached to this submission as promised. A quick search would find a later publication by *Thompson et al* (J Cell Sci 2002;115:2165-77), who teach regulation and mechanism of ferritin translocation. Although *Thompson et al*

did report that ferritin enters the nucleus via active transport through the nuclear pore, the study was performed in human astrocytoma tumor cells, not globin-producing cells. In fact, *Thompson et al* teach that normal astrocytes do not contain ferritin in either cytoplasm or nuclei. Thus, it is unknown and the applicant fails to teach whether the ferritin nuclei translocation in tumor cells applies to normal astrocytes let alone the normal globin-producing cells. Thus, it is improper to use *Thompson et al* supporting the enablement of instantly claimed invention.

Applicant went on accusing the following statement "*is entirely unsupported on the record*", "CURRENTLY, THERE ARE ONLY A HANDFUL OF PAPERS IN THE LITERATURE THAT DESCRIBE THE SUCCESSFUL TRANSDUCTION OF FULL-LENGTH PROTEINS AND REPORT A PHENOTYPE". In response, this statement by the skilled artisan, *Schwarze*, is on record, in a prestige publication reviewing the state of the art at around the instant priority date (page 295, last paragraph).

Applicant then briefly mentioned recent results from the applicant concerning GFP-FtH fusion protein tracks to nucleus, however, such result is not on record, and thus could not be evaluated. Assuming the record is complete with a showing of FtH in the nucleus via FtH protein delivery, the specification fails to teach ferritin-H is actually lacking in the nucleus of globin-producing cells, and supplying extra would then further suppress the β-globin gene expression, and the specification fails to teach how to deliver such in sufficient amount to significant numbers of globin-producing cells in order to obtain clinical benefit, and thus fails to provide an enabling disclosure for what is now claimed.

Applicant named a few protein fragments that could be used as a ligand for globin-producing cell-specific ferritin H delivery. As an initial matter, these fragments were not of record, and not taught by the specification as filed. The specification further fails to teach how to use the ligands, and the mode of operation of the purposed ligand-ferritin-H complex, how the ligand would affect the cell and nucleus entry, the unfolding and refolding processes, and the function of the refolded ferritin-H. The specification fails to address any one of the questions raised by the skilled artisans. Thus, in light of the state of the art and coupled with the instant disclosure, it is reasonable to conclude that the specification fails to provide an enabling disclosure to support the claimed invention.

Applicant also argued that a host immune response to administered ferritin protein is highly unlikely because ferritin is circulating in the blood of all humans. In response, the question of immunogenecity of a protein drug was raised by *Schwarze* concerning the need of engineering a protein for therapeutic purpose such as a fusion protein linking a target domain to the therapeutic domain for cell-specific delivery as has been contemplated by the applicant. Apparently, the Office position is well supported by the state of the art.

The applicant went on to argue that thalassemia is not a hemaoglobinopathy, but refers to a class of diseases resulting from decreased synthesis from otherwise normal globin genes. In response, Applicant's attention is directed to the publication of *Herzog et al* (Expert Rev Cardiovascular Ther 2003;1:215-32), who teach, "SICKLE CELL ANEMIA AND β-THALASSEMIA ARE THE MOST COMMON CLINICALLY RELEVANT β-CHAIN HEMOGLOBINOPATHIES"

(2nd section, page 221), and "β-THALASSEMIA ARISES FROM MORE THAN 200 DISTINCT MUTATIONS THAT AFFECT EVERY STEP IN THE PATHWAY OF GLOBIN GENE EXPRESSION" (3rd section, page 221). *Puthenveetil et al* (Curr Hematology Reports 2004;3:298-305) confirm the teaching *supra*, and state, "THE COMMON HEMOGLOBINOPATHIES TARGETED FOR GENE THERAPY ARE β-THALASSEMIA AND SICKLE CELL DISEASE... β-THALASSEMIAS ARE CAUSED BY ONE OF MORE THAN 200 MUTATIONS OF THE β-GLOBIN GENE, SOME OF WHICH PRODUCE NO β-GLOBIN (β^0) AND OTHERS THAT PRODUCE REDUCED β-GLOBIN (β^+)" (2nd section, page 298, emphasis added). No more needs to be said.

Applicant then acknowledged and speculated that it is *unlikely* the application of ferritin-H for correcting a phenotype of sickle cell disease will result in severe β–thalassemia citing several publications as support. However, these references were not addressing the consequence of suppressing a diseased β-globin gene in sickle cell diseases. Applicant speculated the consequence of suppressing β-globin gene and possible compensation with gamma-globin, however, an enabling disclosure should not be based on speculation particularly for such a complicated in vivo physiological process. It is noted that the applicant failed to place the cited supporting art (Noguchi et al and Poillon et al) on the record of this application, and failed to point out specific section in the cited reference where it supported the applicant's contention.

The applicant went on to assert basically that the novel aspect of the instant invention "is well known in the art that this can be accomplished" (page 12, 1st paragraph). This seems to be illogical since a well-known fact would not be "novel".

Applicant then pointed to the data in the newly submitted declaration. The declaration of Dr. Broyles under 37 CFR § 1.132 has been carefully considered. However, the declaration presented post-filing data showing the induction of endogenous FtH **gene** expression by abscissic acid or transgenic mouse expressing a human FtH gene, which data may provide support for claims of invention groups II or III as filed (see Office action mailed 1/29/03), but not for presently elected invention. Applicant is reminded that the elected invention for prosecution in this application is drawn to introducing the ferritin-H **protein** into globin-producing cells; whereas all of the supporting evidence presented so far are based on introducing a **nucleic acid** encoding FtH into a globin-producing cell, or inducing endogenous FtH gene expression. Since the specification only prophetically contemplates instantly claimed approach, and prior- or post-filing art of record are silent concerning conditions introducing an exogenous FtH protein into the nucleus of a globin-producing cell and performing the role of a gene repressor, and whether such approach would lead to the suppression of the sickle cell disease. Here the critical guidance is lacking in the instant disclosure as filed, thus practicing the claimed invention would require the skilled in the art to find out for themselves whether the invention will achieve what it presumed to, and it would have required undue experimentation for the skilled artisan intending to practice the invention. Hence the disclosure fails to meet the standard set forth under §112, 1st paragraph, because the case law requires that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445

(Fed. Cir. 1991); and "CASE LAW REQUIRES THAT THE DISCLOSURE OF AN APPLICATION SHALL INFORM THOSE SKILLED IN THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT TO FIND OUT HOW TO USE IT FOR THEMSELVES." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

Applicant then asserted that the purposed therapeutic approach is predictable because the effect occurs in people who have sickle cell plus HPFH, a naturally occurring version of the proposed treatment. However, the applicant fails to provide any evidence to this aspect, fails to explicitly teach what is HPFH, and fails teach why these people still suffer from sickle cell disease if it reflects an naturally-occurring version of the proposed treatment. Thus, the argument could not be properly evaluated.

Applicant then challenged that *Mankad* provide support for the position of the Office because he makes the point that much is yet to be done towards effective treatment and it was published 6 months before instant filing date. Applicant went on to argue the effect of chemical reactions of FtH is predictable.

In response, although the known effect of FtH may be predictable in an ex vivo environment, the unknown aspect of FtH function in an *in vivo* environment, where many physiological factors act in concern to bring about different physical phenotypes. The specification fails to teach how to deliver the FtH to sufficient number of globin-producing cells and perform only the known function is still under investigation. *Mankad* was cited to show the state of the art at around the time of instant filing date, which reviewed 50 years of progress in the sickle cell therapy. The Office had pointed out that ferritin-H has not yet entered the picture as a potential or well accepted therapeutic strategy. The applicant fails to show otherwise, and fails to provide evidence

that such state of the art has dramatically changed six months after the *Mankad* publication. Moreover, the *Herzog* publication was published three years after the instant priority date, and the repression of diseased gene with FtH was not on the list of gene therapy for sickle cell diseases (e.g. page 221).

Applicant then attacked the publication of *Meyron-Holtz et al*, and relied on *Thompson et al* as support. In response, it is noted that *Meyron-Holtz et al* was submitted by the applicant to support their position of enablement, where the experiment was conducted on human erythroid precursors, whereas *Thompson et al* reference only applies to cancerous astrocytoma cells, not even normal astrocytes as discussed *supra*. Further, the arguments only reinforce that the metabolism of FtH *in vivo* is complicated, and the claimed invention appears to relied on too many assumptions, which may or may not be proven true in future investigations. It would have required undue experimentation for the skilled in the art intending to practice the invention.

Applicants then allege that the examiner "grossly misinterprets" the enablement requirement by asking for a specific, detailed clinical protocol as stated in page 18 of the previous Office action. In response, page 18 of the previous Office action does not request a specific and detailed clinical protocol, it only cited the decision of the court, In re Glass, 181 USPQ 31, (CCPA 1974), and pointed to the fact that the specification lacks description of conditions and a protocol necessary for practicing the invention without undue experimentation. Nevertheless, lacking any experimental data or protocol supporting the claims drawn to treating sickle cell disease with a FtH protein does tilt the

balance towards non-enablement of the claimed invention when considered as a whole. In *In re Glass*, the court does require the applicant's to provide specific conditions for the claimed process by saying "WHILE THERE IS MORE TO THE SPECIFICATION, IT NEVER BECOMES MORE SPECIFIC WITH RESPECT TO PROCESS DETAILS OR APPARATUS OPERATING CONDITIONS", and "NO EXAMPLE TO ILLUSTRATE THE PRACTICAL OPERATION OF THE PROCESS OR THE APPARATUS IS GIVEN. THE STRONG FEELING ONE GETS FROM READING THE ENTIRE SPECIFICATION IS THAT EITHER APPELLANT DID NOT HAVE POSSESSION OF THE DETAILS OF A SINGLE OPERATIVE PROCESS OR, IF HE DID, HE CHOSE NOT TO DIVULGE THEM". Moreover, *Judge Miller* felt the need to further clarify in a separate concurring opinion text, "ACCORDINGLY, IT CAN BE SEEN THAT THE PHRASE 'SUFFICIENCY OF THE DISCLOSURE' INCORPORATES TWO SEPARATE REQUIREMENTS OF SECTION 112: **THE REDUCTION TO PRACTICE REQUIREMENT**, WHICH MUST BE SATISFIED AS OF THE FILING DATE OF THE APPLICATION; AND THE PUBLIC DISCLOSURE REQUIREMENT (SO THAT THOSE SKILLED IN THE ART CAN PRACTICE THE INVENTION)" (emphasis added). In the instant case, the specification contemplates a process of treating sickle cell disease based on an *in vitro* experiment conducted by transfecting erythroleukemia cells with a nucleic acid encoding ferritin-H, but it fails to describe any condition for targeting a FtH protein to a globin-producing cell, for transporting it to nucleus, for binding efficiency with the diseased β-globin gene, for nuclear retaining capacity of the FtH, for the physiological consequence of the suppressed β-globin gene. At each of these levels, conditions particular to the FtH protein and the intended application may ultimately impair effectiveness of the intended use. Moreover, the specification fails to teach the condition of a patient suitable for receiving such treatment, the means and conditions of administering the FtH protein, the pharmacokinetics of the administered FtH protein,

any phenotypic change of the globin-producing cells *in vitro* or *in vivo*, and clinical consequence of lacking a normal β-globin. Thus, it is reasonable to conclude the disclosure is insufficient to support the claimed invention, and the interpretation of the statutory requirement and the case law is proper.

Applicant went on to challenge a common knowledge of the skilled in the art that it often requires hundreds of studies conducted before a protein drug can be used in the clinic. In response, taking the insulin as an example, U.S. patent 4,582,820 was issued on April 15, 1986, a quick search in PubMed (an incomplete record of biomedical studies) would find 20,551 entries on the subject of "insulin and diabetes". The fact speaks for itself.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is now claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 19, 27 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Adams et al* (New Eng J Med 1998;39:5-11), and as evidenced by *Atkinson et al*

(Biochem Cell Biol 1989;67:52-7, IDS) and *Sowemimo-Coker* (Transfus Med Rev 2002 Jan;16:46-60).

Applicant started out asserting that Atkinson et al was misquoted because the blood cells in this paper are from cold-blooded lower vertebrate, not human, and are from embryonic cells not adult red blood cells.

In response, as an initial matter, it is noted that the claimed invention is not limited to humans only, nor it is limited to the use of adult human blood cells. Thus, it is proper to use Atkinson reference as evidence, which examined red blood cells from adult quail (e.g. paragraph under "Methods", page 53). Further, as taught in *Atkinson et al* and *Harrison et al* (Biochim Biophy Acta 1996;161-203), ferritin molecule is widely present from vertebrates, invertebrates, to bacteria and plants (e.g. §3.1.1 and table 1), and is distributed and synthesized in red blood cells (e.g. figures 1 & 14). To this end, it is noted that the applicant does not discriminate the source of red blood cells when he cited the art of record supporting his argument such as *Dickey et al* (see the following paragraph), who used the red blood cells from a tadpole.

Applicant continued to argue that adult red blood cells contain no ferritin relying on *Theil* and *Dickey* references. However, applicants failed to point to specific passage where the support can be found. A close look of *Dickey et al* (1987) would not find the evidence supporting applicant's argument. To the contrary, *Dickey et al* teach the presence of FtH mRNA is predominant (57%) in erythrocytes compared to liver cells (fig. 1, table 1, and 2nd paragraph, page 7905). Moreover, another post-filing reference is provided for a direct evidence (*Files et al*, J Pediatric Hematol Oncol 2002;24:284-90)

that serum ferritin levels increased lineally with cumulative transfusion volume in humans (e.g. abstract, § Result).

Accordingly, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

Q. JANICE LI, M.D.
PRIMARY EXAMINER

QJL
October 13, 2005